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The Clinicopathologic and Molecular Aspects of Non-Melanoma Skin Cancer

Anthony P. Tufaro[1,4], Nijaguna B. Prasad[2], Anne C. Fischer[3] and Allan D. Hess[4]

[1]*Department of Plastic & Reconstructive Surgery, Johns Hopkins Medical Institutions, Baltimore, MD,*

[2]*Department of Surgery, Johns Hopkins Medical Institutions, Baltimore, MD,*

[3]*Department of Surgery and Cancer Immunobiology Institute, UT Southwestern Medical Center, Dallas TX*

[4]*Department of Oncology, Johns Hopkins Medical Institutions, Baltimore, MD, USA*

1. Introduction

Non-melanoma skin cancer (NMSC) is the most common form of malignancy. The annual incidence of NMSC had previously been estimated to be over one million cases per year in United States.(1) A recent study has shown that estimated burden of NMSC to have increased approximately to 3.5 million annual cases, affecting over 2 million people. (2,3)

Although the burden of NMSC measured in terms of mortality and morbidity is thought to be relatively modest, the direct costs of NMSC are substantial owing to its high incidence. In the US Medicare population, it is considered a major health care problem and among the five most costly cancers to treat based on the actual economics of this disease. (4,5) In fact the estimated treatment costs of NMSC exceeded $500 million/year a decade ago.(6) More common than all other cancers combined, NMSC has been associated metachronously with the development of other malignancies. (7,8)

In general, due to an underappreciation of its increasing prevalence and potential to be highly aggressive, NMSC has been relatively overlooked. While the molecular profiles of melanoma have been well characterized given its stature as the most lethal type of skin cancer, those for NMSC have lagged behind. In this chapter we discuss the numerous types of NMSC, their biologic variability and the various risk factors and etiologies. The etiologies for the subset of NMSC with the most mortality, cutaneous squamous cell carcinoma (cSCC) will be summarized. Despite the fact that the majority of these tumors present at early stages, cSCC accounts for the majority of NMSC deaths and 20% of all skin cancer- related deaths. (9,10) We will review the clinical approach and scientific methodologies that are used to analyze skin biopsies specifically evaluating differential gene transcription between patients who either have a definite propensity to develop cSCC or vary in their susceptibility to developing cSCC. In summary we will introduce where the field stands in the discovery of a molecular profile.

As the most frequent cancer in the US and worldwide, NMSC has been increasing in overall incidence since the 1960's at a rate of 3-8% per year.[11, 12] With over 3.5 million new diagnoses of NMSC per year in the United States, it is both the diversity of types, of which there are 82, and biologic variability in phenotype, that makes the analysis of NMSC even more challenging.[2]

Although the incidence of basal cell carcinoma (BCC) exceeds cSCC by a 5:1 ratio, cSCC is associated with the burden of mortality with a yearly disease-specific mortality rate of 1% per year as reported in the early 1990's.[13] Despite the fact that the majority of these tumors present at an early stage, cSCC accounts for the majority of NMSC deaths and 20% of all skin cancer- related deaths.[9,10] Recurrent NMSC carries a very poor prognosis with only a 50% cure rate.[14] In contrast malignant melanoma is the deadliest at 60% of skin cancer deaths, which explains the primary focus on melanoma, albeit it is the rarest skin cancer at 1% of skin malignancies.[15]

Most suspicious skin lesions are more often evaluated by a primary care physician than a dermatologist, but both face the need to identify if a lesion is malignant, premalignant or benign. To appreciate the breadth of the differential diagnosis, a study of 1215 biopsies from a primary care population were evaluated and 80% were benign lesions, 7% premalignant lesions, including actinic keratoses and lentigo maligna, with 13% being malignant. The malignancies included 73% BCC, 14% SCC, and 12% malignant melanoma.[16] There are multiple precursor skin lesions for NMSC and include Bowen's disease, SCC in situ (erythroplasia of Queyrat), and actinic keratoses.

2. Paradigm shift in staging guidelines

In light of the large number of low risk lesions with a cure rate of greater than 90% for the routine lesion, the significance of an increasing incidence of cSCC is not fully recognized, given the often quoted 5-year recurrence and metastatic rates of 8% and 5%, respectively.[10,17,18] With the diverse spectrum of lesions, clearly grouping the worst subset in with the high incidence of low grade lesions numerically minimizes the poor outcomes associated with the most aggressive lesions. In January 2010, the 7th Edition of the American Joint Committee on Cancer (AJCC) Staging Manual introduced a dramatic paradigm shift in the staging of cSCC to better incorporate known clinical predictors of poor outcome into the classification system and thus better group the diversity of lesions properly. It is this edition that has launched a better rationale to track lesions based on their aggressive characteristics and to more comprehensively stage lesions.

The recent changes to the AJCC Staging Manual focus on identifying clinical parameters that portend a worse prognosis to identify and stage appropriately that subset of cSCC that progresses to metastatic disease.[19] These factors include lesional size (> 2cm), and high risk features including a depth of invasion (>2mm, ≥Clark level IV), perineural invasion, tumor grade (poorly differentiated or un-differentiated), as well as high-risk anatomic sites (See Table 1). Tumor grade alone is significantly associated with mortality given a 5-year cure post therapy of 61.5% for poorly differentiated cSCC compared to 94.6% for well differentiated.[10] High risk histologic features were defined as showing poor differentiation, spindle cell characteristics, necrosis, high mitotic activity and deep invasion.[19] Both the depth of invasion and presence of perineural invasion significantly correlate with prognosis and >4mm thickness or depth of invasion of ≥Clark level IV are associated with a 2 fold increased rate of recurrence or 5-fold increase metastatic rate;

similarly, perineural invasion is associated with a 5-fold increase in both the recurrence rate and metastatic rate.[10,20] Although not identified in the 7th Edition of AJCC, other histologic features are important in prognosis and those include lymphovascular invasion and the presence of inflammatory features such as the presence of eosinophils and plasma cells.[21] cSCC in immunocompromised patients or those that arise in scars, sinus tracts or burns all demonstrate a more aggressive biologic phenotype with a greater metastatic rate of up to 40%.[10,22,24] So not only are subsets with a worse prognosis critical to correctly stage in order to appropriately recognize an unrecognized metastatic potential, but also recurrent disease or persistent disease both portent a worse survival of 78% 5-year survival.[20,25]

Histologic Differentiation
Poor differentiation
Spindle cell characteristics
Necrosis
High Mitotic Activity
Deep Invasion
Depth of Invasion
>2mm
Clark Level ³IV
Perineural Invasion
High Risk Anatomic Sites
Nonglabrous Lip
Ear
Advanced T stage (T3 and T4)
Bony extension or involvement
Maxilla, mandible, orbit, temporal bone
Perineural invasion
Invasion of Skull base
Invasion of axial or appendicular skeleton

Table 1. High Risk Factors For NMSC Tumor Characteristics*

* 7th Edition of American Joint Commission on Cancer Staging Manual (19)

3. Overview of treatment

Standard surgical excision remains the mainstay of treatment of NMSC. The traditional surgical methods include excisional biopsy with appropriate margins or MOHS surgery for areas in which margins are limited by anatomy. These so called critical areas include the commissure of the lip, nasal ala or canthus of the eye as shown in Figure 1. Mohs surgery is a microscopically controlled procedure allowing for the narrowest surgical margin (1mm-1.5mm). Ideally, the Mohs resection should include 100% of the epidermal margin, but often 95% is conventional or at least 70% is accepted for frozen section analysis.[26] A conservative approach such as serial sectioning, proper staining technique, and a conservative Mohs margin (~at least 200 micrometer from the surgical margin) can assure the lowest recurrence rate. The use of frozen sections for margin control increases the cure rate of conventional surgical excision to be comparable with Mohs excisions.

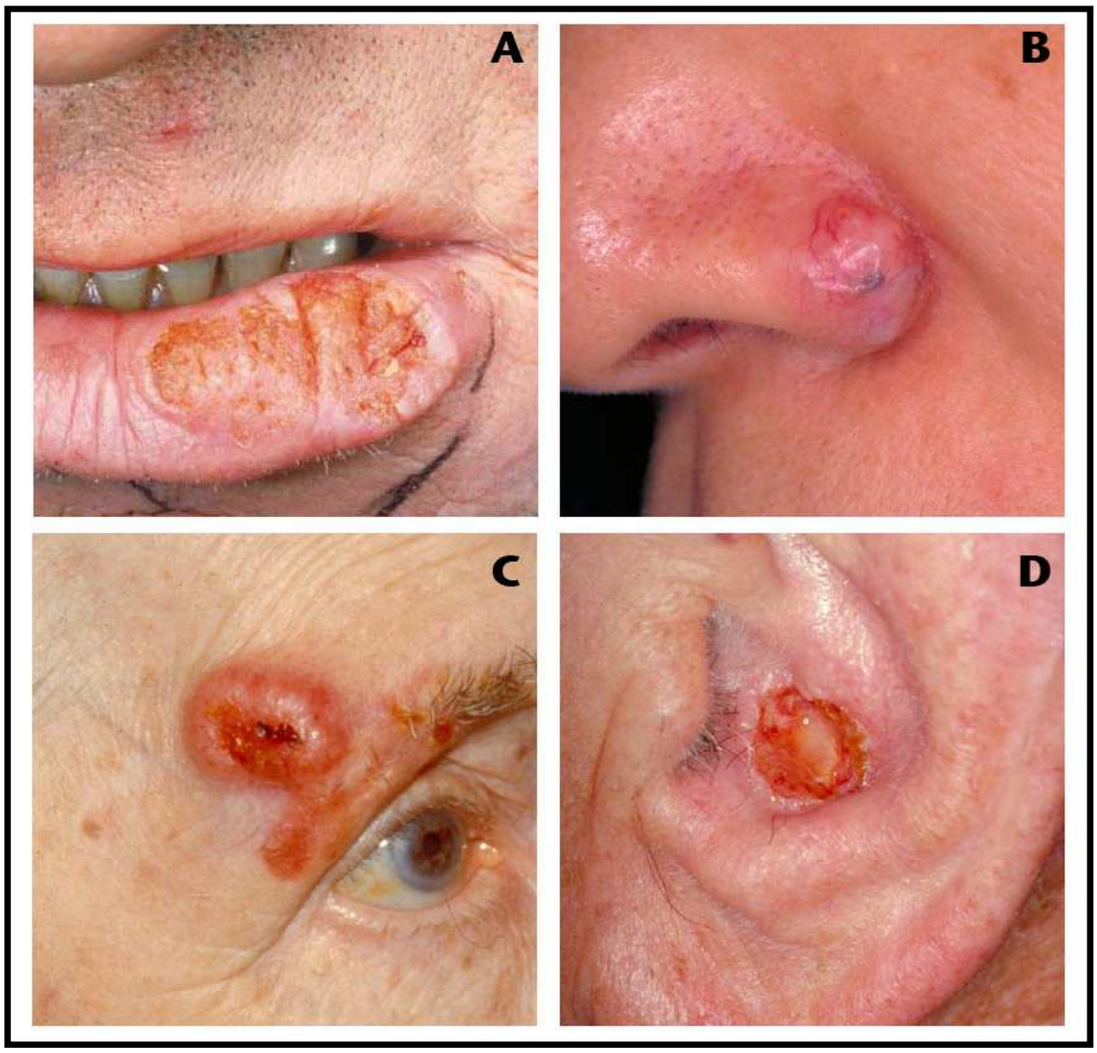

Fig. 1. Clinical presentations of Non-melanoma Skin cancer cutaneous squamous. Cell carcinoma (A and D) Basal Cell Carcinoma (B and C). Courtesy from Skin Cancer Guide CA.

Larger lesions should be biopsied with an incisional technique. A scalpel or a 2 or 3 mm. dermatologic punch can be used. The biopsy should avoid any area that appears to contain necrotic tissue. It is often best to biopsy at the apparent margin of the malignant lesion with normal skin. The biopsy should be "full thickness", including epidermis, dermis and subcutaneous tissue. This will allow adequate evaluation of the depth of invasion and allow for surgical planning. Small lesions can be excised with a 0.5 to 1 cm. margin. Larger lesions will require a 1cm. or wider margin

Traditional histology of skin tissue uses vertical sectioning with the subcutaneous tissue at the bottom and the epidermis at the top. In contrast, Mohs surgery uses tangential or horizontal sectioning. Thus the samples from biopsies are typically formalin-fixed paraffin-embedded tissue blocks or frozen tissue specimens from Mohs surgery. These tissue specimens are first analysed for histologic review or evaluated by Mohs mapping. The mapping combined with the unique "smashing the pie pan" method of processing such that the corollary of the blood covered surgical margin is an aluminum pie pan. The top of the pie is the crust covered surface of the skin and the goal is to flatten this specimen into one flat sheet, mark it, stain it, and examine it under the microscope.[27]

Notably there are many nonsurgical modalities, including cryosurgery, electrodessication and curettage, radiotherapy and intralesional therapies. However, all these later approaches lose the benefit of pathologic analysis. Thus it is easy to understand why capturing the actual incidence of NMSC has been difficult. In the era of personalized medicine, molecular markers have been used in many tumors to prognosticate and risk stratify patients. Given the relative lack of recognition of the growing incidence of cSCC and the inability to track the worst subset of cSCC given the abundance of low risk lesions and the practice of not banking or staging lesions, these molecular studies have been relatively limited compared to the field of melanoma.

4. Risk factors

Multiple etiologies exist for cSCC, including environmental, genetic, altered immunity and virally mediated. The high incidence of cSCC and BCC is primarily attributed to sun exposure and the mutagenic effects of ultraviolet (UV) light worsened by geographic latitude.[11,28] Cutaneous SCC and BCC are more common in fair skinned patients and anatomic sites exposed to the sun, such as head, neck and extremities: head and neck is the most common site. Other known risk factors are male sex, advanced age, immunosuppression (induced or acquired), human papilloma viruses (HPV), chronic inflammation and genetic diseases manifested in the skin.[28-30] Genetically inherited skin conditions that have a known propensity of risk for developing cSCC are albinism, xeroderma pigmentosum, and epidermodysplasia verruciformis.[9,31-32] The strongest risk factors for NMSC mirror the etiologies and include Caucasian race, older age 55-75 years of age, male sex, a prior diagnosis of NMSC confers a 10-fold risk for recurrence, and immunosuppression, as well as genetic, chemical and environmental factors (See Table 2). Likewise sites of chronic inflammation, such as scars, sinus tracts, and burns, can also demonstrate more aggressive clinical behavior and a greater propensity to metastasize with an overall metastatic rate of 40%.[10,22]

Significant Risk Factors
Caucasian
Immunosuppression
Previous NMSC or precursor lesion
Age 55-75
Male sex
Genetic Risk Factors
Blue eyes
Fair skin
Celtic ancestry
Genetic Syndromes
Xeroderma Pigmentosum
Albinism
Epidermodysplasia verruciformis
Basal cell nevus syndrome
Chemical Exposure
Coal Tar
Tobacco
Environmental Exposure
Ionizing radiation
Primary Inflammatory skin disorder
Chronic wounds, burns, scars

Table 2. Potential Risk Factors for NMSC

5. Immunologic altered host state

Several studies have demonstrated an association between an enhanced risk of NMSC and immunosuppression in patients with inflammatory bowel disease (IBD), rheumatoid arthritis (RA) and solid-organ transplants.[33- 35] Malignant lesions develop within 10 years after organ transplantation. The prevalence of NMSC in renal transplant recipients (RTR) is 5% and from 10% to 27% at 2 and 10 years, respectively, but increases up to 40% to 60% at 20 years.[36] In the long-term follow-up, this represents an increase of 12 to 90 times the NMSC-risk in the general population.[35] Similarly, in heart transplant recipients, the cumulative risk rose from 4.3% at 1 year up to 43.8% at 7 years after transplantation.[37,38]

More importantly, the incidence and risk of malignancy particularly cSCC is significantly elevated in post-transplant patients compared to other patient populations. Immunosuppression is associated with a disproportionate increase in the incidence of cSCC of up to 64-250 times greater than that in the general population compared to the 10-fold increased risk in BCC. This disproportionate increase causes a reversal of the expected 5:1ratio of BCC: cSCC in immunocompetent individuals to a range between 1:1.8 and 1:15 in those that are immunosuppressed.[39,40]

Furthermore, immunosuppression significantly impacts the biology and aggressiveness of cSCC. In solid organ transplant patients, cSCC tumors tend to be numerous, exhibit a strong propensity to recur and metastasize at a high rate regardless of lesional size.[41] Skin malignancies in transplant recipients has some features that differ from those in the general population; (i) multiple sites are involved, (ii) the cancers occur in younger age-group (30 years vs. 60 years), (iii) the cancers are more aggressive and recur more frequently, and (iv) the squamous cell type is more common than basal cell.[42]

6. Viral pathogenesis

The increased incidence of cSCC in immunocompromised patients compared to BCC suggests a mechanism of viral pathogenesis. Evidence of HPV has been reported in cSCC in organ transplant patients with up to 80% of lesions containing HPV DNA as well as the presence of a higher viral load of HPV DNA.[43,44] However the variable quantity of HPV in immunocompetent individuals can range between 27-70% depending on detection techniques.[32,44] Thus the type of HPV, β-papillomavirus species 2, may be more often associated with cSCC as opposed to the total amount of HPV DNA present.[32]

Three theories have been suggested for the mechanism of HPV carcinogenesis: 1) UV radiation induced immunosuppression to explain an enhanced interaction between HPV and UV radiation, 2) E6/E7 oncoprotein-related changes in p53 and Rb tumor suppressor gene, and 3) integration of HPV DNA disrupting genomic stability.[32,45,46]. Viral expression of E6 and E7 oncoproteins can inactivate p53 and Rb tumor suppessor genes, leading to an uncontrolled system of cell proliferation and apoptosis.[47]

Association of viral pathogens such as human papillomavirus (HPV) with head and neck squamous cell cancer (HNSCC), especially oropharyngeal cancer has been recognized over the past two decades. HPV16 is the most common genotype in these tumours, whereas HPV6 and HPV11 can also be found in a minority of these cancers, implying that these low-risk HPV types are not entirely benign in HNSCC. HPV DNA is closely associated with poorly differentiated cancers, positive lymph nodes and late-stage disease, which portend a worse diagnosis. HPV status is also associated with p16 expression and HPV+ tumours are less likely to harbour p53 mutations.[48] A subset of HNSCC patients who had HPV 16 infection confers a better prognosis. On the other hand, β papillomaviruses (β- HPVs) also play a role in the tumorigenesis of cSCC as shown by both European and US studies.[49] However, no high-risk types have been identified although there is an association of β species 1 in SCC. Other viruses, such as polyomavirus (MCPyV) have been shown to be causative agent in Merkel cell carcinoma.[50]

7. Allelic imbalance and loss of heterozygosity

The genetic progression model for head and neck squamous cell carcinoma (HNSCC) demonstrates that loss of heterozygosity (LOH) is common during the progression from

premalignant lesion to malignant tumors.[51] Tumor suppressor genes (TSGs) are usually found in the area of loss rendering the cells more susceptible to tumorigenesis.[52]
Several regions of chromosomal loss are identified in HNSCC. One of the most common regions, 9p21, has been reported in both HNSCC and cSCC.[53,54] This region contains several TSGs, including p16INK4A (CDKN2A), p15INK4B and MTAP. Allelic imbalances are also found in other regions of cSCC, including LOH on 3p, 2q, 8p, and 13 and allelic gain on 3q and 8q.[55] Such studies indicate that allelic imbalance and LOH are recognized and relevant events in cSCC and can be used for early diagnosis and tumor surveillance.

8. Epigenetics

Epigenetics is the inheritance of genetic information that is altered in gene expression without changes in the DNA sequence. Epigenetic alterations include DNA methylation and histone modifications, which consist of methylation, acetylation, phosphorylation, ubiquitination, and sumoylation. Changes in genomic DNA methylation associated with cancer include global DNA hypomethylation and gene-specific hyper- or hypomethylation. All of these modifications of gene expression have been associated with the development of various tumor types, including HNSCC and cSCC.[56,57] A higher frequency of FOXE1 promoter hypermethylation has been documented in SCCs (55%) which was seen in association with a complete absence of or downregulated gene expression, indicating that FOXE1 is a crucial player in development of cutaneous SCC.[56]
Promoter DNA methylation gene panels have been described for screening of primary HNSCC, for determination of tumor recurrence, and assessment of margin status during surgery.[58,59] However, a determination of methylation gene panels relevant in cSCC is yet to be established. A combination of different genes from different pathways may allow for a better determination of the aggressiveness of cSCC to determine prognosis.

9. RNA and MiRNA

Messenger RNA (mRNA) and microRNA (MiRNA) profiles have been described in both HNSCC and cSCC.[60] MiRNAs play a role in regulation of mRNA. Several mRNA biomarkers for cSCC were identified, including CCR10, CCL27, MUC4, p16, MMP2 and MMP9.[61] A recent study has demonstrated that a distinct microRNA profile is modulated by UV radiation.[62]

10. Mitochondrial mutation

Mitochondrial mutation in HNSCC has been well reported; however, only a few studies show the association of mitochondrial DNA mutation and cSCC.[63] Several regions of mitochondrial DNA were reported, including displacement-loop (D-loop) and other regions.[64,65] Therefore, mitochondrial mutations may correlate in the future with the phenotypic behavior of cSCC.

11. Conclusions

The molecular mechanisms that underlie the development of cutaneous skin cancers are poorly understood. Even the spectrum of biologic behavior has been slow to be

characterized given the previously very generic clinical criteria used to distinguish low risk lesions from more aggressive lesions. Recent changes in the classification of the staging paradigm have better captured this more aggressive subset to allow for a more precision in identifying the worst subset. Thus molecular analysis can potentially profile that subset with biomarkers chosen to best correlate with the biologic phenotype.

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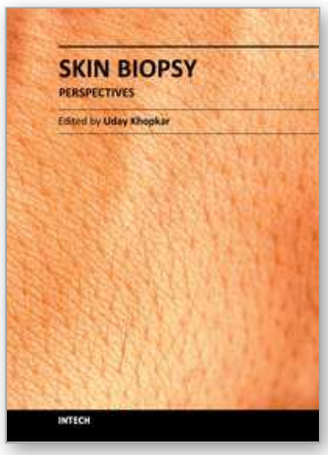

Skin Biopsy - Perspectives

Edited by Dr. Uday Khopkar

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Skin Biopsy - Perspectives is a comprehensive compilation of articles that relate to the technique and applications of skin biopsy in diagnosing skin diseases. While there have been numerous treatises to date on the interpretation or description of skin biopsy findings in various skin diseases, books dedicated entirely to perfecting the technique of skin biopsy have been few and far between. This book is an attempt to bridge this gap. Though the emphasis of this book is on use of this technique in skin diseases in humans, a few articles on skin biopsy in animals have been included to acquaint the reader to the interrelationship of various scientific disciplines. All aspects of the procedure of skin biopsy have been adequately dealt with so as to improve biopsy outcomes for patients, which is the ultimate goal of this work.

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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